Phase II, open-label, randomized trial of the MEK1/2 inhibitor selumetinib as monotherapy versus temozolomide in patients with advanced melanoma

Kirkwood, J M ; Bastholt, L ; Robert, C ; Sosman, J ; Larkin, J ; Hersey, P ; Middleton, M ; Cantarini, M ; Zazulina, V ; Kemsley, K ; Dummer, R

Abstract: PURPOSE: To compare the efficacy and tolerability of the mitogen-activated protein (MAP)/extracellular signal-regulated (ERK) kinase (MEK) 1/2 inhibitor selumetinib versus temozolomide in chemotherapy-naive patients with unresectable stage III/IV melanoma. EXPERIMENTAL DESIGN: This phase II, open-label, multicenter, randomized, parallel-group study examined the effect of 100 mg oral selumetinib twice daily in 28-day cycles versus oral temozolomide (200 mg/m(2)/d for 5 days, then 23 days off-treatment). The primary endpoint was progression-free survival. RESULTS: Two hundred patients were randomized. Progression-free survival did not differ significantly between selumetinib and temozolomide (median time to event 78 and 80 days, respectively; hazard ratio, 1.07; 80% confidence interval, 0.86-1.32). Objective response was observed in six (5.8%) patients receiving selumetinib and nine (9.4%) patients in the temozolomide group. Among patients with BRAF mutations, objective responses were similar between selumetinib and temozolomide groups (11.1% and 10.7%, respectively). However, five of the six selumetinib partial responders were BRAF mutated. Frequently reported adverse events with selumetinib were dermatitis acneiform (papular pustular rash; 59.6%), diarrhea (56.6%), nausea (50.5%), and peripheral edema (40.4%), whereas nausea (64.2%), constipation (47.4%), and vomiting (44.2%) were reported with temozolomide. CONCLUSIONS: No significant difference in progression-free survival was observed between patients with unresectable stage III/IV melanoma unselected for BRAF/NRAS mutations, who received therapy with selumetinib or temozolomide. Five of six patients with partial response to selumetinib had BRAF mutant tumors. Clin Cancer Res; 18(2); 555-67. ©2011 AACR.

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John M. Kirkwood, Lars Bastholt, Caroline Robert, et al.

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Phase II, Open-Label, Randomized Trial of the MEK 1/2 Inhibitor Selumetinib as Monotherapy *Versus* Temozolomide in Patients With Advanced Melanoma

John M. Kirkwood[1], Lars Bastholt[2], Caroline Robert[3], Jeff Sosman[4], James Larkin[5], Peter Hersey[6], Mark Middleton[7], Mireille Cantarini[8], Victoria Zazulina[8], Karin Kemsley[8], Reinhard Dummer[9]

Authors' affiliations:

[1] Departments of Medicine and Dermatology, University of Pittsburgh; Melanoma Program, University of Pittsburgh Cancer Institute, Pittsburgh, Pennsylvania, USA

[2] Department of Oncology, Odense University Hospital, Odense, Denmark

[3] Department of Medicine, Institut Gustave Roussy, Villejuif, France

[4] Vanderbilt Ingram Cancer Center, Nashville, Tennessee, USA

[5] Royal Marsden Hospital, Department of Medicine, London, UK

[6] Newcastle Melanoma Unit, Newcastle, New South Wales, Australia

[7] NIHR Biomedical Research Centre, Churchill Hospital, Oxford

[8] AstraZeneca, Alderley Park, Macclesfield, UK

[9] Department of Dermatology, Zürich University Hospital, Zürich, Switzerland

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Corresponding author:
Professor John M. Kirkwood
University of Pittsburgh Cancer Institute
HCC Suite 1.325117 Center Avenue
Pittsburgh, PA 15213-1863
Tel: +412-623-7707
Fax: +412-623-7704
Email: KirkwoodJM@upmc.edu

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Translational relevance

The Ras/Raf/MEK/ERK pathway is a key signaling cascade driving cell cycle proliferation, differentiation and survival. Activations in this pathway contribute to malignant progression in many human cancers. Selumetinib (AZD6244/ARRY-142886) is an oral inhibitor of MEK1/2 currently in clinical development for a number of tumor types. Preclinical studies have demonstrated antitumor activity of selumetinib in melanoma xenograft models particularly those harboring BRAF mutations. In this study there was no significant difference in efficacy between the selumetinib and temozolomide as first-line therapy for patients with advanced melanoma not selected for activating BRAFmutations. Of note, five of the six patients showing partial response with selumetinib had tumors that were BRAF mutant. Based on these results, and preclinical data, a phase II study of selumetinib in combination with chemotherapy for patients with BRAF-mutated melanoma has been initiated.

Abstract

Purpose: To compare the efficacy and tolerability of the MEK 1/2 inhibitor selumetinib versus temozolomide in chemotherapy-naïve patients with unresectable stage III/IV melanoma.

Methods: This phase II, open-label, multicenter, randomized, parallel-group study examined the effect of 100 mg oral selumetinib twice daily in 28-day cycles versus oral temozolomide (200 mg/m^2/day for 5 days, then 23 days off treatment). The primary endpoint was progression-free survival.

Results: Two hundred patients were randomized. Progression-free survival did not differ significantly between selumetinib and temozolomide (median time to event 78 and 80 days, respectively; hazard ratio, 1.07; 80% confidence interval, 0.86–1.32). Objective response was observed in six (5.8%) patients receiving selumetinib and nine (9.4%) patients in the temozolomide group. Among patients with *BRAF* mutations, objective responses were similar between selumetinib and temozolomide groups (11.1% and 10.7%, respectively). However, five of the six selumetinib partial responders were *BRAF* mutated. Frequently reported adverse events with selumetinib were dermatitis acneiform (papular pustular rash; 59.6%), diarrhea (56.6%), nausea (50.5%) and peripheral edema (40.4%), whereas nausea (64.2%), constipation (47.4%) and vomiting (44.2%) were reported with temozolomide.

Conclusions: No significant difference in progression-free survival was observed between patients with unresectable stage III/IV melanoma unselected for BRAF/NRAS mutations, who received therapy with selumetinib or temozolomide. Five of six patients with partial response to selumetinib had *BRAF* mutant tumors.

Introduction

The Ras/Raf/MEK/ERK pathway is a key signaling cascade driving cell cycle proliferation, differentiation and survival (1, 2). Mutations affecting signaling molecules, including Ras and Raf, activate this pathway and contribute to malignant progression in many human cancers (3-6). *BRAF* and *NRAS* mutations are generally mutually exclusive in melanoma (7, 8). At the time of study initiation the mutation frequencies for *BRAF* and *NRAS* were estimated as 59% (9) and 30% (10) respectively. However, recent estimates suggest that the frequency for *BRAF* mutations may be as low as 41% (11).

Agents targeting mutated *BRAF* are in development (12, 13); however, they may be associated with paradoxical activation of the MAPK pathway in BRAF wild-type cells (14). MEK1/2 is an attractive therapeutic target due to its key position within the Ras/Raf/MEK/ERK pathway (2, 15) and paradoxical activation effects are not expected with MEK inhibitors. Selumetinib (AZD6244/ARRY-142886) is an orally available, potent, selective, allosteric inhibitor of MEK1/2 with preclinical antitumor activity in melanoma (16), which has been shown to inhibit the growth of cell lines expressing *BRAF* V600E mutation (17, 18).

In a phase I trial of selumetinib including patients with melanoma (20/57 patients, 35%), prolonged stable disease (SD) ≥5 months was observed in nine patients (16%) (19). The maximum tolerated dose of selumetinib was determined as 200 mg BID however, the dose chosen for ongoing phase II studies was 100 mg BID due to the frequency of treatment-related rash with chronic administration. Consistent inhibition of ERK phosphorylation shown between pre- and post-treatment biopsies demonstrated that this dose results in target inhibition. This study also showed that selumetinib 100mg BID was considered to have a manageable toxicity profile.

The current study compared the efficacy of orally administered selumetinib and temozolomide (TMZ) in chemotherapy-naïve patients with advanced melanoma. It is the first

multicenter, randomized study conducted in patients with melanoma assessed for both *BRAF* and *NRAS* mutations. At the time of initiation there was no global standard of care for chemotherapy-naïve advanced melanoma patients, therefore TMZ was chosen as comparator for this study because it had been used in both clinical trials and was licensed for this indication in some countries (20). In addition, TMZ has the same active metabolite (5-[3-methyl-1-triazeno]imidazole-4-carboxamide) as dacarbazine, an approved treatment for advanced melanoma, but TMZ has the benefit of being administered orally. The dose of TMZ (200 mg/m^2/day for 5 days, followed by 23 days off treatment) used in the present study is the recommended monotherapy dose (21) which was used in a large phase III study in patients with advanced melanoma (22).

Methods

This phase II, open-label, multicenter, randomized, parallel-group study (clinicaltrials.gov registry number NCT00338130) enrolled patients without previous systemic chemotherapy for advanced melanoma between July 2006 and June 2007, and was conducted in accordance with good clinical practice guidelines and the Declaration of Helsinki. Thirty-four centers from 10 countries participated in this trial: Argentina (3 centers), Australia (3), Austria (2), Brazil (6), Canada (2), Denmark (1), France (3), Switzerland (1), the United Kingdom (3) and United States (10).

Patient selection

All included patients provided written informed consent and fulfilled the following criteria: age ≥18 years, histologic or cytologic confirmation of unresectable American Joint Committee on Cancer (AJCC) stage III or IV malignant melanoma, at least one measurable site of disease defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0, World Health Organization (WHO) performance status 0–2 and willingness to provide tumor biopsy (fresh or archival) for determination of *BRAF* and *NRAS* mutation status. Female patients were required to have a negative pregnancy test or be postmenopausal. To be representative of the general melanoma population, the number of uveal melanoma patients was limited to 20 of the planned 182.

Exclusion criteria included absolute neutrophil count <1,500/mm^3, platelets <100,000/mm^3, hemoglobin ≤9 g/dL, serum creatinine clearance ≤30 mL/min, serum bilirubin ≥1.5 x upper limit of normal (ULN), aspartate aminotransferase ≥2.5 x ULN, alanine aminotransferase ≥2.5 x ULN or serum creatinine ≥1.5 mg/dL, chemotherapy or radiotherapy within 5 years prior to start of study treatment (excluding palliative radiotherapy at focal sites), any systemic chemotherapy for unresectable AJCC stage III or IV melanoma, prior combination biochemotherapy for cancer, unstable brain metastasis or spinal cord compression (<3 months off steroids), and history of another primary malignancy within 5 years prior to

start of study treatment (except for adequately treated basal or squamous cell skin cancer or cancer of the cervix *in situ*).

Study design

Patients were randomized 1:1 to selumetinib (100 mg free-base solution, twice daily in 28-day cycles) or TMZ (200 mg/m^2/day for 5 days, followed by 23 days off treatment). Assessment by RECIST criteria was performed at weeks 6 and 12, and then every 8 weeks for progression-free survival (PFS). Local center tumor assessment was used for the primary analysis, with conclusions validated by an independent central review of scans/images. Patients could continue study treatment until objective disease progression (defined by local investigator) and were then followed for survival. Patients with progressive disease (PD), as assessed by the investigator in the TMZ group, were permitted to crossover to selumetinib.

Data cut-off was 28 September 2007 for PFS and objective tumor response. All other analyses, including time-to-death (TTD) used a date of 20 June 2008.

Study objectives

The primary objective was to compare the efficacy of selumetinib versus TMZ in patients with unresectable stage III or IV malignant melanoma. The primary outcome was PFS. Secondary outcomes were TTD, objective response rate (ORR) and duration of response.

PFS, defined as the interval between the date of randomization and the first date of objective disease progression (RECIST 1.0) or death due to any cause, was to be analyzed following approximately 126 progression events. Non-progressing patients were censored at last objective tumor assessment.

TTD was calculated from randomization until death due to any cause; surviving patients were censored at last date known to be alive, or withdrawal of consent.

Best objective response (OR) (complete response [CR], partial response [PR], SD ≥6 weeks) or PD was calculated as the best response, using RECIST 1.0, recorded from date of randomization.

Secondary objectives included assessment of safety, tolerability, and efficacy of selumetinib versus TMZ with respect to *BRAF* or *NRAS* mutation status.

Exploratory analyses included assessment of the treatment effect in the following subgroups; disease stage (Stage III *v* Stage IV), uveal melanoma *v* non-uveal, mucosal melanoma *v* non-mucosal, and *BRAF* and *NRAS* mutation status.

Assessment of safety

Adverse events (AEs), serious AEs (SAEs), clinical laboratory evaluations, vital signs and electrocardiograms were collected from provision of informed consent until 30 days after discontinuation of study treatment. AEs were collected using Common Terminology Criteria for Adverse Events (CTCAE) Version 3.

Determination of *BRAF* and *NRAS* mutation status

Pathology review confirmed the presence of tumor; no enrichment by macro-dissection was performed prior to DNA extraction, given the high sensitivity of the allele-specific polymerase chain reaction (PCR)-based method ARMS™ (Amplification Refractory Mutation System). The methods used for mutation detection including sequences of primers and probes for detection of *BRAF* and *NRAS* mutations have been previously described (23). The allele-specific PCR detects BRAF V600E as well as V600K and V600D (1799T>A), the allele-specific PCR for NRAS detects NRAS Q61K mutation (C181A) and the Q61R mutation (A182G). Mutation testing was carried out centrally within the AstraZeneca tumor genetics research laboratory.

In brief, genomic DNA was extracted from thin sections totaling 40 μm by digestion in proteinase K for 48 h, boiling in 5% chelex, phase-extracting in chloroform, ethanol-precipitating and resuspending in 100 μl water. PCR was performed as described previously, utilizing cell line admixtures containing the mutation of interests to act as positive controls (23).

A mutation-positive result was only accepted if it was present in two independent PCRs generated from the same DNA sample. Normal genomic DNA was used as a negative control. Results were not designated positive unless the mutation was detected at a level above the non-specific background noise. This was done in order to control for false-positive results. A 'negative' result from an assay could represent no mutation present; if there was insufficient DNA extracted from the sample to identify the presence of the mutation it was designated a fail.

Determination of *GNAQ* mutation status

GNAQ analysis was performed in uveal melanoma tumors only. Codon 209 was analyzed by ARMS™ and direct sequencing. The same forward primer was used for both sequencing and ARMS™: 5'-ACTGTAAAACGACGGCCAGTTTTTCCCTAAGTTTGTAAGTAGTGCT-3'. Reverse primers were used as follows: *GNAQ* sequencing reverse, 5'-ACCAGGAAACAGCTATGACCGTCTGACTCCACGAGAACTTGAT-3'; *GNAQ* 209P ARMS™ reverse, 5'-AGTGTATCCATTZTCTTCTCTCTGACCTTP-3'; *GNAQ* 209L ARMS™ reverse, 5'-AGTGTATCCATTZTCTTCTCTCTGACCTTE-3' (L=LNA [locked nucleic acid] modified C, P=LNA G, Z=LNA T).

Statistical and analytical methods

A sample size of 182 patients (91 per arm) was required to provide adequate power for comparison of PFS between the two treatment groups both in the overall population and in the *BRAF* mutant subpopulation (24). Patients with *BRAF* mutant tumors (assumed to be

60% of the total) (9) were hypothesized to show a greater response to selumetinib than those with wild-type tumors. The target PFS hazard ratio (HR) in the *BRAF* mutant subgroup was 0.67 (and was to be tested as a secondary endpoint at the one-sided significance level of 20%).

To maintain statistical power for the overall population, the target HR on which the study was powered was 0.74 for PFS (i.e., a 35% delay in median time to progression assuming exponential distribution). This assumed that the *BRAF* wild-type subpopulation contained *NRAS* mutant patients (approximately 30%), who might derive clinical benefit.

This study was designed to have 80% power to detect a true PFS HR of 0.74 in the overall population at the one-sided 20% significance level, and required approximately 126 progression events. The trial was designed as a randomized screening trial to quantify the level of risk entailed for further development, and as such the Type I and Type II errors were adjusted to be less constrained, so that the targeted treatment benefit may be appropriate while the sample size remains reasonable (25) (as discussed by Rubinstein LV et al 2005).

PFS and TTD were analyzed using a Cox Proportional Hazards model allowing for the effect of treatment and fitting for the following baseline covariates: *BRAF* mutation status (positive *v* negative *v* unknown), WHO performance status (0 *v* 1 or 2), tumor type (non-uveal [cutaneous, mucosal, unknown] *v* uveal) and level of lactate dehydrogenase (<2 x ULN *v* ≥2 x ULN) at baseline. These covariates were thought to be potentially prognostic and thus the impact of these covariates is adjusted for in the statistical analyses in order to improve the precision of the estimated treatment effect as well as compensating for any lack of balance between groups for these baseline covariates. The model included these effects regardless of whether the inclusion of effects significantly improved the fit of the model. These analyses were pre-specified in the Statistical Analysis Plan. Tumor stage (III vs. IV) was pre-specified as a covariate but not included in the model as only six patients had an unresectable AJCC stage III tumor.

Intention-to-treat (ITT) analysis was used for all efficacy analyses. The ITT population included all randomized patients and compared the treatment groups on the basis of randomized treatment, regardless of the treatment actually received. The evaluable-for-safety population was a subset of the ITT population that included all patients who received ≥1 dose of study treatment and was used for summaries of the safety data.

Results

Demographics and other patient characteristics

Two hundred and thirty-nine patients were enrolled, of whom 200 were randomized: 104 to selumetinib and 96 to TMZ (Fig. 1). Of these patients, 99 and 95 received selumetinib and TMZ, respectively. Ninety-six and 92 patients, respectively, discontinued assigned treatment with selumetinib or TMZ. Three patients in each arm were continuing assigned treatment at the time of data cut-off. Fifty-nine patients in the TMZ arm switched to selumetinib. In total, 158 randomized patients (79.0%) had their *BRAF* and *NRAS* mutation status confirmed. *BRAF* mutant tumors were identified in 73/158 patients (46.2%) (V600E – 66, V600K – 5, K601E – 1, K581S – 1); 28/158 patients' tumors (17.7%) were *NRAS* mutated (Q61K – 15, Q61R – 12, G13R – 1). No tumors were both *BRAF* and *NRAS* mutated; therefore, 101/158 patients' tumors (63.9%) were either *BRAF* mutant or *NRAS* mutant. Of the 42 patients without confirmed mutation status, 24 did not have samples to analyze and 18 had no result due to assay failure.

The study population was representative of the advanced melanoma clinical population in terms of baseline and demographic characteristics; however, there were some imbalances between the treatment arms (Table 1). There was a higher percentage of women in the selumetinib group (47.1%) than in the TMZ group (32.3%). In addition, more patients were *BRAF* mutant in the selumetinib group (43.3%) than in the TMZ group (29.2%), and more patients in the selumetinib group had WHO performance status 1 or 2 compared with those receiving TMZ (33.7% and 26.1%, respectively).

In the *BRAF* and *NRAS* mutant subpopulation, more patients had WHO performance status 1 or 2 in the selumetinib group (38.2%) than in the TMZ group (23.9%). Furthermore, more *BRAF* or *NRAS* mutant patients in the selumetinib group (12.7%) had lactate dehydrogenase levels ≥2 x ULN compared with those in the TMZ group (8.7%). The analyses adjusted for these factors.

Twenty (10%) patients in the study had uveal melanoma, with 15 evaluable for *BRAF*/*NRAS* mutations; no mutations in BRAF or NRAS were detected. Twelve patients with uveal melanoma had tumors with sufficient material evaluable for *GNAQ* mutation: four tumors were *GNAQ* mutated (three GNAQ 209P, one GNAQ 209L), eight tumors were *GNAQ* wild-type.

Efficacy

Progression-free survival based on investigator assessed RECIST data

The PFS analysis was performed after 151 progression events. No difference in PFS was observed between selumetinib and TMZ (HR 1.07; 80% confidence interval [CI]: 0.86–1.32; 1-sided p=0.650; 2-sided p=0.699) (Fig. 2A). In pre-specified analyses, PFS was consistent across subgroups (data not shown) except for patients with uveal melanoma (HR 0.70; 80% CI: 0.35–1.42) but no significant difference could be concluded for patients with uveal melanoma due to the small number of patients (16 events/20 patients) and wide CI. Overall, 79 (76%) patients in the selumetinib group and 72 (75%) patients randomized to TMZ had objective disease progression or had died at the data cut-off point, with median time to event of 78 and 80 days, respectively.

Due to open-label nature of the study an independent central review was incorporated to assess consistency and ensure that conclusions were robust. Discordance between the disease status assessment in local and central review was noted, with local review more favorable for selumetinib (Supplemental Table 1) (26). In 20% of cases, the discrepancy was due to different assessments of percentage change of target lesions alone and 31% were due to the identification of one or more new lesions alone (Supplemental Table 2) either by the local review or by central review. This discordance did not change the conclusions of this study.

Time to death

The final analysis of TTD was performed after 130 deaths had occurred. The median TTD was 284 and 369 days for selumetinib and TMZ groups, respectively (HR: 1.351; 80% CI: 1.07–1.71; 95% CI: 0.95–1.93; 1-sided p=0.950; 2-sided p=0.099) (Table 2), suggesting improved but not statistically significant TTD for TMZ compared with selumetinib in the overall population (Fig. 2B). A higher proportion of patients randomized to TMZ received selumetinib following disease progression (61%) compared with those who received TMZ or dacarbazine following progression on selumetinib (≥24%). The frequency of crossover from selumetinib to TMZ may be an underestimation as this information was not mandatorily gathered as part of the study protocol.

Objective response rate based on investigator assessed RECIST data

Statistical comparisons of ORR and duration of response were not formally performed due to the low number of responses. The number of patients with confirmed PR was 5.8% (6/104) for patients in the selumetinib group and 9.4% (9/96) in the TMZ group (Table 3). No CRs were observed in either group. Forty-eight (46.2%) patients in the selumetinib group had SD of ≥6 weeks' duration compared with 36 (37.5%) in the TMZ group. At the time of the overall survival analysis, two new PRs were observed in patients with wild-type tumors randomized to TMZ and one TMZ patient with a previous PR became a CR. Of the 11 responders in the TMZ group, the duration of response ranged from 94 to ≥420 days (three patients were still responding at time of data cut-off). In the selumetinib group the duration of response ranged from 130 to 358 days (all patients had progressed).

Efficacy in patients with BRAF or NRAS mutations

There were no significant differences in PFS between the two treatment groups in the *BRAF*-mutant (Fig. 2C) and *BRAF*- or *NRAS*-mutant subsets (not shown). Among patients with *BRAF* mutation, objective tumor response was observed in 11.1% (5/45) of patients

receiving selumetinib and 10.7% (3/28) of the TMZ group. Similarly, in the patient subpopulation with *BRAF* or *NRAS* mutations, the objective tumor responses were 9.1% (5/55) and 8.7% (4/46) in the selumetinib and TMZ groups, respectively (Table 3). Of the six selumetinib responders, five were *BRAF* mutant compared with three of the nine TMZ responders. As with the overall population, *BRAF* mutant patients randomized to TMZ had improved TTD compared with those randomized to selumetinib (Fig. 2D).

Efficacy in patients who switched treatment

As of 28 September 2007, 51 patients randomized initially to TMZ had switched to selumetinib; 46 (90.2%) switched following objective disease progression and five patients switched incorrectly (before objective disease progression as assessed by site RECIST data). Three switches were due to an incorrect assessment of objective disease progression and the other two resulted from clinical progression alone (the latter two patients went on to progress according to RECIST 28 days and 64 days after switching to AZD6244; the first patient had new lesions and the second died).

As of 20 June 2008, 59 of the 96 patients randomized to TMZ (61%) had switched to selumetinib (54/59 patients after objective disease progression). No further patients had incorrectly switched prior to disease progression. One patient (2%) had PR, 25 (46%) had PD and 8 (15%) were not evaluable. Two patients who switched exhibited PR while receiving selumetinib; however, one of these switched prior to objective disease progression on TMZ and so is counted as a response to TMZ. The patient with confirmed PR on selumetinib following progression to TMZ was *BRAF* mutant.

Change in tumor size

Exploratory plots were produced to assess the change from baseline in tumor size by week 6 and best overall change at time of primary analysis (Supplemental Fig.1). Overall there

was little difference between the two treatment groups for change in tumor size, either at week 6 or for best overall change.

Safety

Adverse events

Most AEs reported in this study were CTCAE Grade 1 or 2 and were manageable with drug holiday or standard supportive therapy (Table 4). Fewer patients in the TMZ group had treatment-related AEs, AEs ≥ Grade 3, SAEs or AEs leading to discontinuation compared with the selumetinib group. The most frequent SAEs in the selumetinib group were diarrhea (n=3), vomiting (n=3) and infections (n=3). Small intestinal obstruction (n=2) and confusional state (n=2) were the most frequent SAEs in the TMZ group. Three deaths were reported in patients receiving selumetinib; one death due to unknown cause occurred in the absence of tumor progression, one patient died of metastases to meninges (disease progression) and one patient experienced cardiorespiratory arrest that was attributed to selumetinib by the investigator. A further selumetinib-randomized patient died outside of the 30-day follow-up reporting period as a result of myocarditis.

The most commonly reported AEs were dermatitis acneiform (59.6%), diarrhea (56.6%) and nausea (50.5%) in the selumetinib group, and nausea (64.2%), constipation (47.4%) and vomiting (44.2%) in the TMZ group (Table 4).

Laboratory evaluation

Deterioration in hematology parameters of at least two grades from baseline was observed in fewer patients treated with selumetinib than with TMZ; leukocytes (1.0% *v* 8.5%), lymphocytes (6.1% *v* 14%), neutrophils (2.0% *v* 7.5%) and platelets (1.0% *v* 11.7%).

A greater proportion of patients receiving selumetinib demonstrated deterioration of at least two grades from baseline in clinical chemistry parameters than with TMZ: alanine

aminotransferase (13.1% *v* 3.2%), aspartate aminotransferase (11.8% *v* 2.4%) and albumin (16.3% *v* 1.1%). Bilirubin levels remained normal in both treatment groups.

A slight increase in calcium-phosphate product level was observed in the selumetinib group, with six patients reporting levels above the pre-defined cut-off (4.5 mmol/L). One of these patients had an SAE (Grade 3) of hyperphosphatemia.

Small increases in mean systolic (7.4 mmHg) and diastolic (5.3 mmHg) blood pressure, without a corresponding change in heart rate, were observed in the selumetinib group by week 8. Hypertension was reported as an AE by eight (8.1%) patients in the selumetinib group and two (2.1%) in the TMZ group.

Discussion

Advanced melanoma represents one of the most treatment-refractory malignancies. Despite decades of research, worldwide consensus on a standard first-line treatment has yet to be established. While dacarbazine and TMZ are used for first-line chemotherapy of advanced melanoma, patient response to these agents is low (22, 27). The present study investigated the role of the oral MEK1/2 inhibitor selumetinib as monotherapy for patients with unresectable stage III/IV melanoma. No significant difference was seen in the primary endpoint of PFS between the two treatment arms for either the overall population or the subpopulations of patients with *BRAF* or *BRAF/NRAS* mutant tumors. Although some imbalances were seen between treatment groups in baseline covariates, the statistical analyses adjusted for the impact of these factors. Disease control (5.8% PR; 46.2% SD) with selumetinib monotherapy was observed. Because of the open-label nature of this trial, an independent central review of tumor assessment was incorporated to ensure consistency. However, as stated in the protocol, the primary efficacy analysis was based on the investigator-assessed RECIST data as this was considered to be more reflective of clinical practice and the central review was not carried out in real time. As has been reported for other studies (28), differences between local and central review were noted but this did not alter the conclusions of the primary analyses.

Tumor responses to selumetinib monotherapy have been observed in patients with melanoma and other solid tumors, suggesting anti-tumor activity with this MEK1/2 inhibitor. Cell lines expressing *BRAF* or *RAS* mutations (including melanoma cell lines) have increased sensitivity to selumetinib (29). This is particularly relevant to melanoma since recent estimates suggest that activating mutations of *BRAF* and *NRAS* are found in 41% and 18% of melanomas, respectively (11). Although the present study did not test for mutation status prospectively, 79% of patients had mutation status confirmed retrospectively. Retrospective mutation testing could be considered a limitation of this study given the imbalance seen between treatment arms. However, the rationale for pre-specified

retrospective testing was 2-fold: firstly, implementing prospective testing of patients would require central testing in a time frame that might withhold treatment from patients for a prolonged period of time, and secondly the primary objective was to assess efficacy in the overall population, and so making patients wait for a mutation test before starting treatment, when the result would not exclude them from entering the trial, was felt not to be in the patients' best interests.

The observed *BRAF* mutation rate of 46.2% is lower than had been expected when planning this study but similar to recent reports (11, 30, 31). Of note in our study, five of the six patients showing PR with selumetinib had tumors that were *BRAF* mutant. This finding raises the possibility that *BRAF* mutation may be an important, but not exclusive, requirement for response to selumetinib. Data from other compounds in development have shown that patients with *BRAF* mutant tumors can show a high response rate to MEK or BRAF inhibition (12, 13, 32-34). For example, a phase I trial of the MEK inhibitor GSK112012 demonstrated disease control in eight of eleven patients with *BRAF* mutant melanoma (32). This suggests that additional genetic markers may be necessary for a cell to respond to selumetinib monotherapy. In line with this hypothesis, a transcriptional profile associated with activation of MEK and sensitivity to selumetinib pre-clinically has recently been identified, although this may not be predictive of clinical benefit (35). Testing performed on samples from this study showed no correlation between this transcription profile and clinical response (AstraZeneca, data on file).

The clinical challenge is, therefore, to find ways of optimizing the efficacy of selumetinib, for example through combination with other targeted agents or chemotherapy. In preclinical models, selumetinib in combination with docetaxel, irinotecan, gemcitabine or TMZ was shown to have enhanced anti-tumor efficacy compared with single-agent treatment (36). Preliminary clinical results from a phase I trial of selumetinib in combination with either dacarbazine, docetaxel or temsirolimus have demonstrated objective response in five out of nine patients with *BRAF* mutation-positive tumors (37). Selumetinib is currently being

investigated for advanced melanoma in combination with dacarbazine for patients with prospectively determined *BRAF* mutant tumors (NCT00936221).

Possible theories for the non-significant improved survival of patients initially assigned to TMZ versus selumetinib (other than a chance finding) were examined, but no clear explanation was found. Firstly, selumetinib might have had a detrimental effect in relation to survival, but no differences in other efficacy endpoints (PFS, ORR, change in tumor size) and safety data did not suggest this, either in this trial or a separate comparative phase II trial measuring TTD (38). Secondly, an imbalance in prognostic factors might have contributed to this outcome, but this is unlikely since imbalances in a range of prognostic factors (lactate dehydrogenase, WHO performance status, *BRAF* mutation status and tumor type) had already been accounted for in the TTD analysis. Thirdly, an imbalance in the number of patients that crossed over from TMZ to selumetinib, or vice versa, (61% TMZ arm versus ~25% selumetinib arm) could have affected the outcome; for example, the possibility that the sequential administration of two equally active agents prolonged survival (selumetinib has activity that is preliminarily in the range of TMZ, and PFS curves are not dissimilar). However, the relative activity of these agents in the first- and second-line setting is unknown. Additionally, the relative activity of non-study treatments that non-crossover patients went on to receive after TMZ and selumetinib is unknown.

To be representative of the general melanoma population, patients with uveal melanoma were included in this study. It was felt that these patients have the potential to benefit from MEK inhibition because they may carry somatic mutations such as GNAQ and GNA11 (39). Analysis of efficacy in these patients was an exploratory endpoint that did not translate into a significant clinical benefit in this trial. However, based on anecdotal evidence from this and a Phase I study (19), a Phase II study of selumetinib in patients with uveal melanoma has been initiated, NCT01143402.

Selumetinib was generally well tolerated; the reported AEs were consistent with prior reports (19, 40), and no new clinically significant safety issues were identified in the present study. There was a higher reported incidence of dermatitis acneiform, diarrhea and peripheral and periorbital edema with selumetinib than with TMZ. Nausea, vomiting, constipation, dyspnea and fatigue were more commonly reported in the TMZ group than in the selumetinib group, which is consistent with the prescribing information for TMZ. Hematological toxicities were not an issue with selumetinib.

Dermatological toxicities with selumetinib resemble those observed with epidermal growth factor receptor inhibitors (41) in their clinical presentation (dermatitis acneiform, xerosis cutis, paronychia) (40). These skin toxicities can be ameliorated by topical corticosteroid and/or antibacterial therapy (40, 42) and responded to dose interruptions or discontinuation of therapy. In the present study, selumetinib-associated dermatologic conditions were manageable; only one patient discontinued study treatment due to dermatitis acneiform. It has been suggested that there may be a link between rash and the signal transduction pathway. An exploratory (unplanned) analysis of rash (maximum grade on treatment) and efficacy (maximum change in tumor size) found no relationship (AstraZeneca, data on file).

The toxicity profile of selumetinib in this trial therefore appears to be manageable. However, it is possible that the acceptable tolerability of selumetinib may be a consequence of under-dosing in this study and could, therefore, explain the low number of responses observed. During development of selumetinib the dose-limiting toxicities and maximum tolerated dose were based on the frequency of rash. It is possible that in the subsequent development of newer MEK inhibitors, lessons were learnt from these early trials of selumetinib and other MEK inhibitors, and the management of rash that results from administration of this type of drug is now more effective. For example, in a phase I trial of the MEK inhibitor GSK1120212 which had disease control rate of 73%, the frequency of rash was 77% (43). However, the frequency of grade 3 rash was lower than that seen in our study, suggesting that although the incidence of rash may be higher overall it could be better controlled with optimal

supportive care. It is therefore possible that the dose of selumetinib used in this phase II study was overcautious with regard to toxicity and that the maximal dosage range was not explored in full. It should therefore be noted that ongoing and future trials of selumetinib will use a 75 mg hydrazine-sulfate tablet formulation which demonstrates statistically significantly higher plasma exposure as well as oral bioavailability 197% that of the 100 mg free-base suspension used in this study (44).

In conclusion, the oral MEK1/2 inhibitor selumetinib showed modest activity with no significant difference in PFS compared with TMZ in chemotherapy-naïve, patients with advanced melanoma unselected for BRAF mutations. The objective tumor responses observed were comparable in both the overall and *BRAF* and *NRAS* mutant populations; however, five out of six selumetinib responders had *BRAF* mutant tumors. Further development of selumetinib in this disease will therefore focus on combination with other agents and upon the selection of patients for therapy, using *BRAF* mutation status.

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Table 1. Patient demographics and baseline characteristics

	Treatment group	
	Selumetinib (n = 104) n (%)	**Temozolomide (n = 96)** n (%)
Sex		
Male	55 (52.9)	65 (67.7)
Female	49 (47.1)	31 (32.3)
Age, years		
Mean (range)	57.1 (20-84)	57.0 (28-84)
Racial origin		
Caucasian	99 (95.2)	91 (94.8)
Non-Caucasian[a]	3 (2.9)	3 (3.0)
Unknown	2 (1.9)	2 (2.1)
WHO performance status		
0 Normal activity	67 (64.4)	71 (74.0)
1 Restricted activity	34 (32.7)	23 (24.0)
2 In bed ≤ 50% of the time	1 (1.0)	2 (2.1)
Unknown	2 (1.9)	0 (0)
AJCC staging		
Stage III	3 (2.9)	3 (3.1)
Stage IV	99 (95.2)	92 (95.8)
M1a/b	40 (38.5)	36 (37.5)
M1c	58 (55.8)	54 (56.3)
Unknown M status	1 (1)	2 (2.1)
Unknown stage	2 (1.9)	1 (1.0)
Lactate dehydrogenase level at baseline[e]		
<2 x ULN	79 (76.0)	79 (82.3)
≥2 x ULN	17 (16.3)	15 (15.6)
Unknown	8 (7.7)	2 (2.1)
Tumor type		
Cutaneous	75 (72.1)	72 (75.0)
Uveal	7 (6.7)	13 (13.5)
Mucosal	6 (5.8)	0 (0.0)
Unknown primary tumor	16 (15.4)	11 (11.5)

Mutation status		
BRAF positive	45 (43.3)	28 (29.2)
NRAS positive	10 (9.6)	18 (18.8)
Wild-type for both	29 (27.9)	28 (29.2)
Unknown[b]	20 (19.2)	22 (22.9)

[a] This group comprised Black, Hispanic and Mediterranean patients.

[b] This group comprised those patients where there was no result for both *BRAF* and *NRAS* mutation status or one of the mutation assays failed.

Abbreviation: ULN, upper limit of normal.

Table 2. Summary of time-to-death analysis for selumetinib *v* temozolomide in the overall population and in *BRAF* and *NRAS* mutant patients

	Number of patients	Number of deaths (%)	Median time to event (days)	Hazard ratio[a]	Confidence interval		p-value	
					2-sided 80%	2-sided 95%	1-sided[b]	2-sided
Overall population[c]								
Selumetinib	104	73 (70.2)	284	1.351	1.07, 1.71	0.95, 1.93	0.950	0.099
Temozolomide	96	57 (59.4)	369					
***BRAF*-mutant subpopulation[d]**								
Selumetinib	45	34 (75.6)	284	1.654	1.12, 2.45	0.91, 3.02	0.949	0.102
Temozolomide	28	16 (57.1)	369					
***BRAF*- and *NRAS*-mutant subpopulation[d]**								
Selumetinib	55	42 (76.4)	275	1.621	1.18, 2.23	0.99, 2.65	0.973	0.053
Temozolomide	46	27 (58.7)	383					

[a] Hazard ratio <1 indicated a benefit for selumetinib.

[b] The 1-sided p-value indicated whether selumetinib was associated with longer time-to-death than temozolomide.

[c] Analyzed using Cox Proportional Hazards model adjusted for: lactate dehydrogenase (LDH), *BRAF* mutational status, WHO performance status and primary tumor type.

[d] Analyzed using the Cox Proportional Hazards model adjusted for: LDH and WHO performance status.

Abbreviations: LDH, lactate dehydrogenase; WHO, World Health Organization.

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Table 3. Objective tumor response for selumetinib and temozolomide

Response status	Objective tumor response	Treatment group	
		Selumetinib n (%)	Temozolomide n (%)
Overall population		**n = 104**	**n = 96**
Response[a]	Complete response	0	0
	Partial response	6 (5.8)	9 (9.4)
	Total	6 (5.8)	9 (9.4)
Non-response	Stable disease ≥6 weeks	48 (46.2)	36 (37.5)
	Progressive disease	40 (38.5)	43 (44.8)
	Non-evaluable	10 (9.6)	8 (8.3)
	Total	98 (94.2)	87 (90.6)
***BRAF* mutant subpopulation**		**n = 45**	**n = 28**
Response[a]	Complete response	0	0
	Partial response	5 (11.1)	3 (10.7)
	Total	5 (11.1)	3 (10.7)
Non-response	Stable disease ≥6 weeks	18 (40.0)	12 (42.9)
	Progressive disease	17 (37.8)	11 (39.3)
	Non-evaluable	5 (11.1)	2 (7.1)
	Total	40 (88.9)	25 (89.3)
***BRAF* and *NRAS* mutant subpopulation**		**n = 55**	**n = 46**
Response[a]	Complete response	0	0
	Partial response	5 (9.1)	4 (8.7)
	Total	5 (9.1)	4 (8.7)
Non-response	Stable disease ≥6 weeks	23 (41.8)	21 (45.7)
	Progressive disease	21 (38.2)	19 (41.3)
	Non-evaluable	6 (10.9)	2 (4.3)
	Total	50 (90.9)	42 (91.3)

[a] An objective response included patients with either a confirmed complete response or partial response according to Response Evaluation Criteria in Solid Tumors Version 1.0.

Table 4. Most frequent all-causality adverse events (occurring in at least 15% of patients in each group), serious adverse events and discontinuations due to any adverse events

	Number (%) of patients			
	Selumetinib n = 99		Temozolomide n = 95	
Preferred term	**AE**	**AE ≥ Grade 3**	**AE**	**AE ≥ Grade 3**
AE	**99 (100.0)**	**57 (57.6)**	**92 (96.8)**	**36 (37.9)**
Dermatitis acneiform	59 (59.6)	12 (12.1)	3 (3.2)	0 (0.0)
Diarrhea	56 (56.6)	4 (4.0)	20 (21.1)	0 (0.0)
Nausea	50 (50.5)	3 (3.0)	61 (64.2)	3 (3.2)
Peripheral edema	40 (40.4)	1 (1.0)	6 (6.3)	3 (3.2)
Fatigue	29 (29.3)	3 (3.0)	40 (42.1)	4 (4.2)
Vomiting	28 (28.3)	1 (1.0)	42 (44.2)	6 (6.3)
Headache	21 (21.2)	3 (3.0)	23 (24.2)	2 (2.1)
Pyrexia	16 (16.2)	1 (1.0)	10 (10.5)	0 (0.0)
Constipation	12 (12.1)	0 (0.0)	45 (47.4)	1 (1.1)
Serious AEs	**32 (32.3)**		**16 (16.8)**	
Discontinuations due to AEs	**10 (10.1)**		**2 (2.1)**	

This table includes adverse events with an onset date between the date of the first dose and 30 days following the date of the last dose of study treatment (unless the patient switched to selumetinib earlier than 30 days following discontinuation of temozolomide).

Abbreviation: AE, adverse event.

Table legends

Table 1. Patient demographics and baseline characteristics

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Figure legends

Fig. 1. Patient disposition.

Fig. 2. Comparison of progression-free survival, (A) and (C), and of time-to-death, (B) and (D), between selumetinib and temozolomide in the overall population (A) and (C) and BRAF mutant patients, (B) and (D).

Abbreviations: HR, hazard ratio; CI, confidence interval

Figures

Fig. 1. Patient disposition

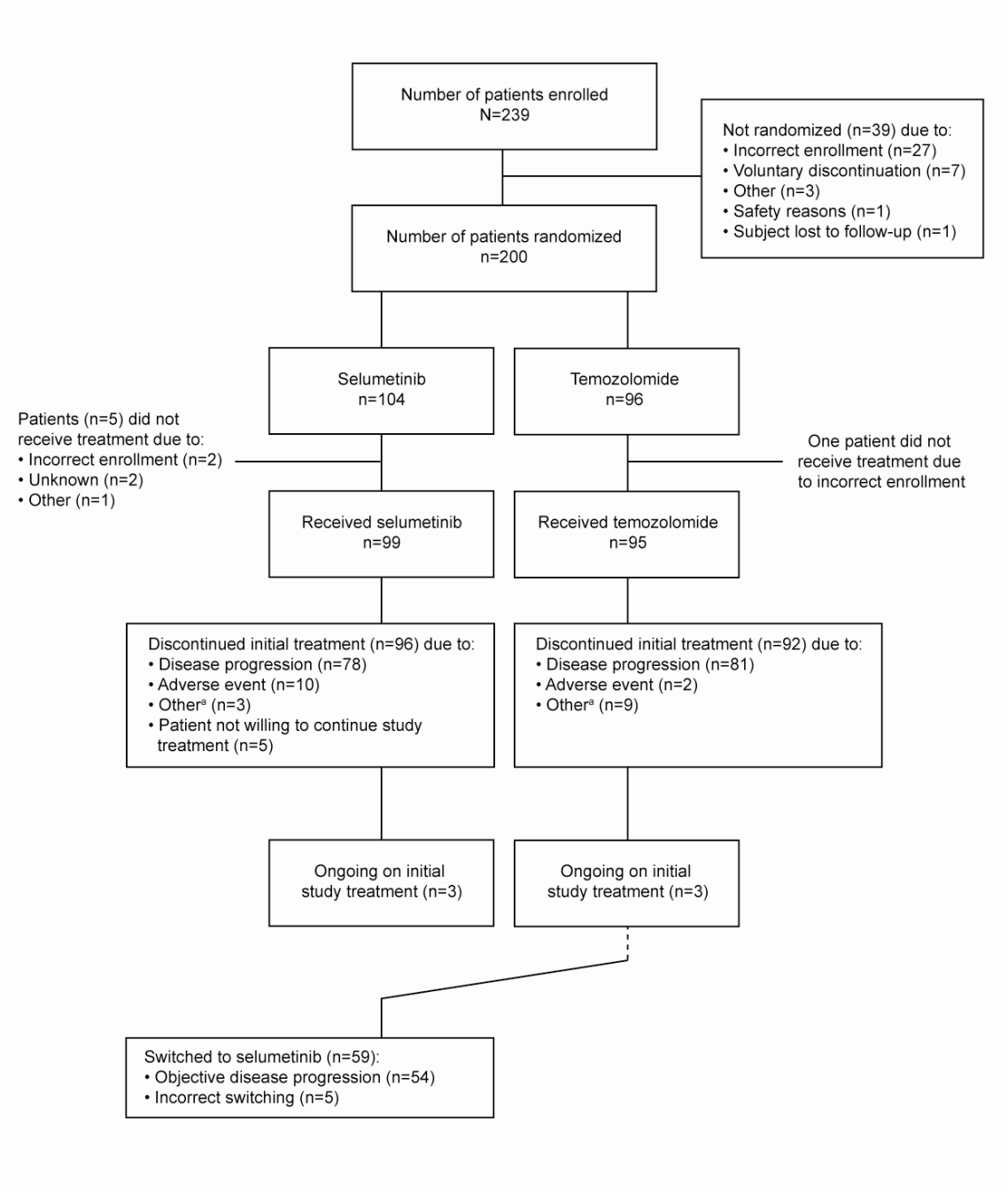

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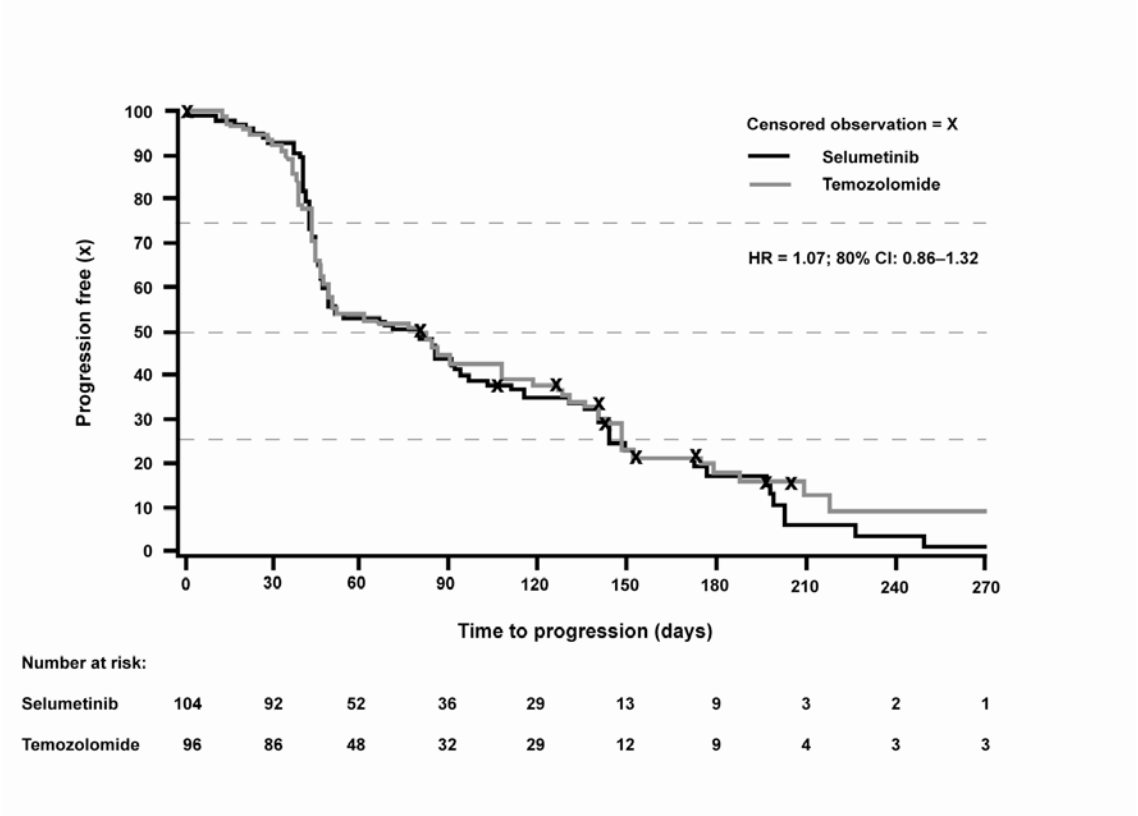
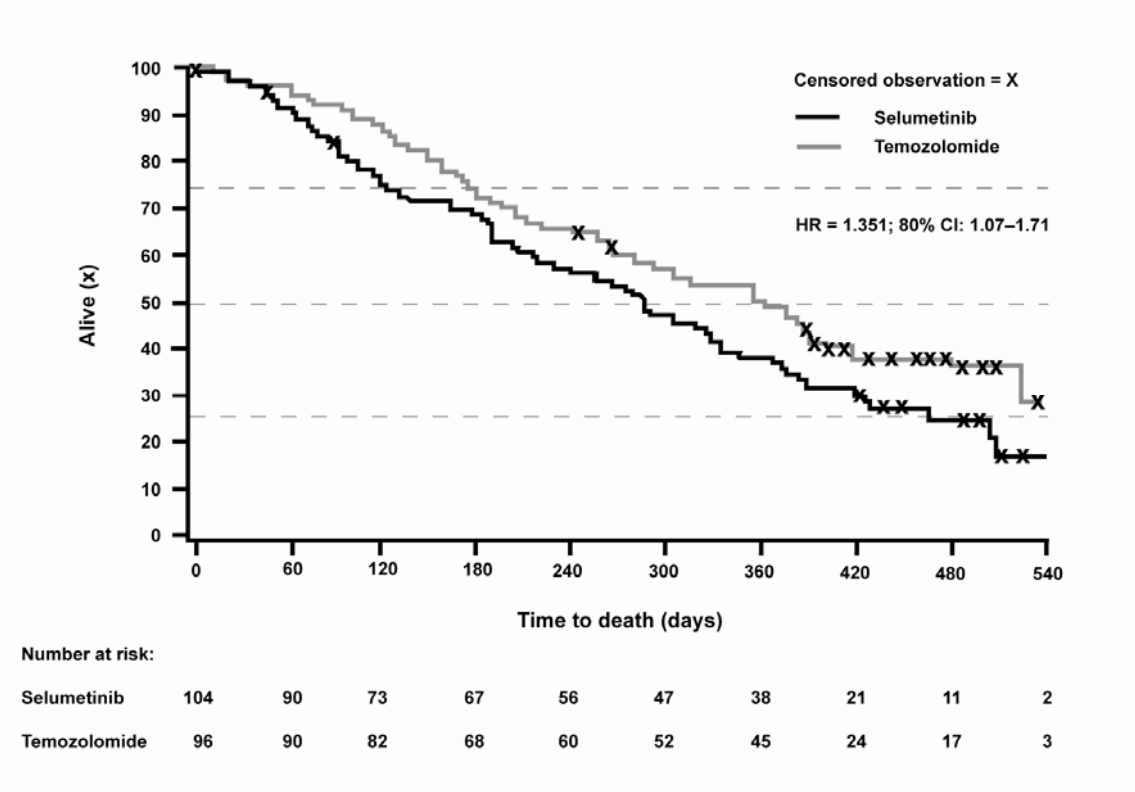
Fig. 2. Comparison of progression-free survival, (A) and (C), and of time-to-death, (B) and (D), between selumetinib and temozolomide in the overall population (A) and (C) and BRAF mutant patients, (B) and (D).

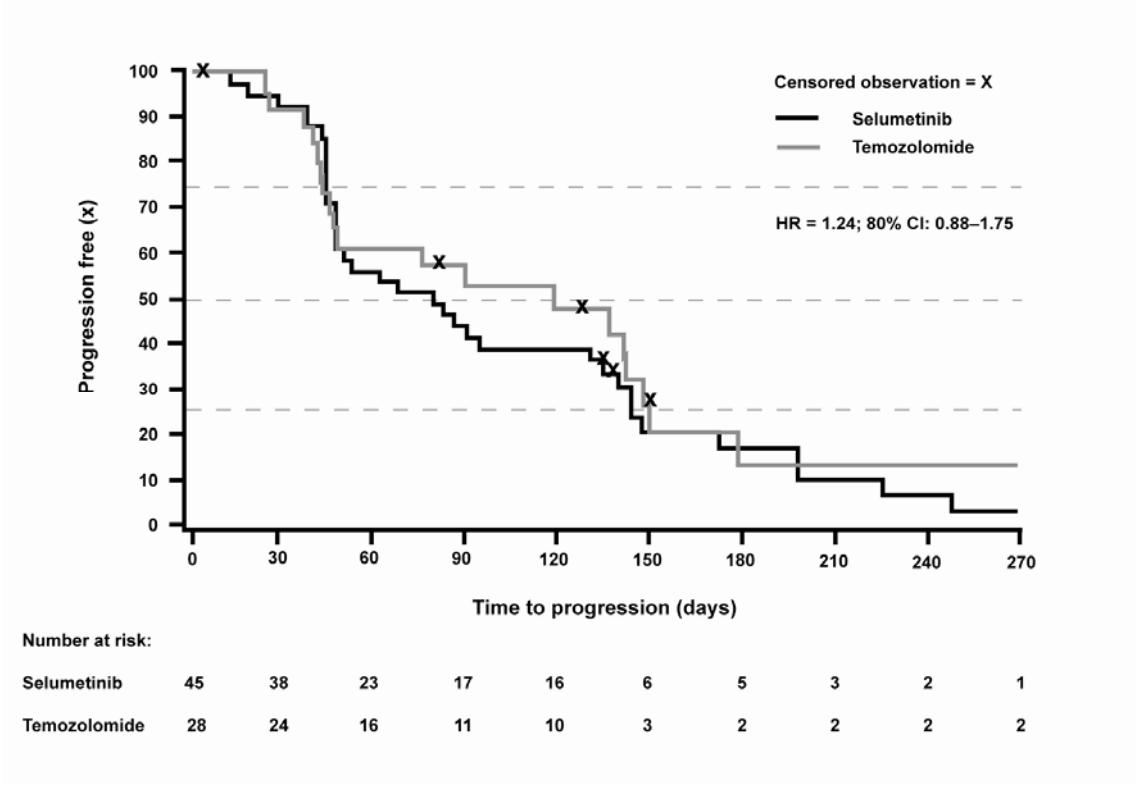
A) Kaplan–Meier comparison of progression-free survival between selumetinib and temozolomide in the overall population (intent-to-treat population).



(B) Kaplan–Meier comparison of time-to-death between selumetinib and temozolomide in the overall population (intent-to-treat population).



(C) Kaplan–Meier comparison of progression-free survival between selumetinib and temozolomide in the *BRAF* mutant subpopulation (intent-to-treat population).



Author Manuscript Published OnlineFirst on November 2, 2011; DOI:10.1158/1078-0432.CCR-11-1491
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

(D) Kaplan–Meier comparison of time-to-death between selumetinib and temozolomide in the *BRAF* mutant subpopulation (intent-to-treat population).

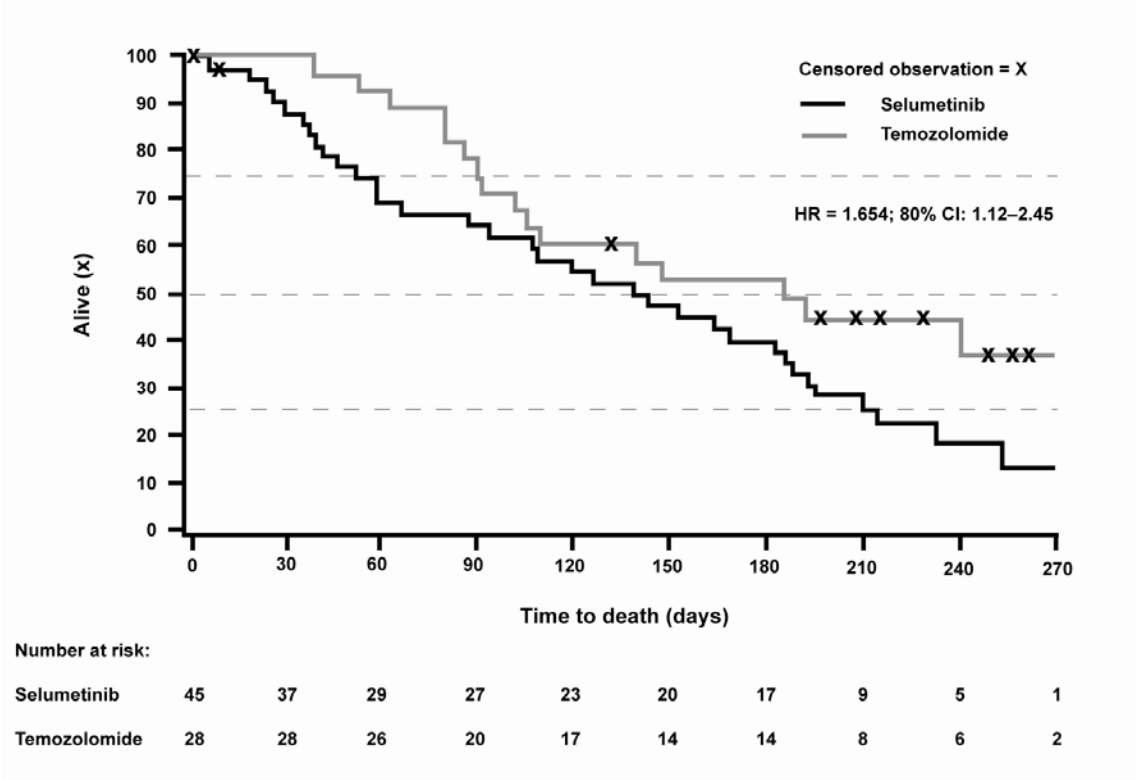


Table 1.

	Treatment group	
	Selumetinib (n = 104)	**Temozolomide (n = 96)**
	n (%)	**n (%)**
Sex		
Male	55 (52.9)	65 (67.7)
Female	49 (47.1)	31 (32.3)
Age, years		
Mean (range)	57.1 (20-84)	57.0 (28-84)
Racial origin		
Caucasian	99 (95.2)	91 (94.8)
Non-Caucasian[a]	3 (2.9)	3 (3.0)
Unknown	2 (1.9)	2 (2.1)
WHO performance status		
0 Normal activity	67 (64.4)	71 (74.0)
1 Restricted activity	34 (32.7)	23 (24.0)
2 In bed ≤ 50% of the time	1 (1.0)	2 (2.1)
Unknown	2 (1.9)	0 (0)
AJCC staging		
Stage III	3 (2.9)	3 (3.1)
Stage IV	99 (95.2)	92 (95.8)
M1a/b	40 (38.5)	36 (37.5)
M1c	58 (55.8)	54 (56.3)
Unknown M status	1 (1)	2 (2.1)
Unknown stage	2 (1.9)	1 (1.0)
Lactate dehydrogenase level at baseline[e]		
< 2 x ULN	79 (76.0)	79 (82.3)
≥ 2 x ULN	17 (16.3)	15 (15.6)
Unknown	8 (7.7)	2 (2.1)
Tumor type		
Cutaneous	75 (72.1)	72 (75.0)
Uveal	7 (6.7)	13 (13.5)
Mucosal	6 (5.8)	0 (0.0)
Unknown primary tumor	16 (15.4)	11 (11.5)
Mutation status		
BRAF positive	45 (43.3)	28 (29.2)
NRAS positive	10 (9.6)	18 (18.8)
Wild-type for both	29 (27.9)	28 (29.2)
Unknown[b]	20 (19.2)	22 (22.9)

[a] This group comprised Black, Hispanic and Mediterranean patients.

[b] This group comprised those patients where there was no result for both *BRAF* and *NRAS* mutation status or one of the mutation assays failed.

Abbreviation: ULN, upper limit of normal.

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Table 2.

	Number of patients	Number of deaths (%)	Median time to event (days)	Hazard ratio[a]	2-sided 80% CI	p-value (1-sided)[b]
Overall population[c]						
Selumetinib	104	73 (70.2)	284			
Temozolomide	96	57 (59.4)	369	1.351	1.07, 1.71	0.95
***BRAF* mutant subpopulation[d]**						
Selumetinib	45	34 (75.6)	284			
Temozolomide	28	16 (57.1)	369	1.654	1.12, 2.45	0.949
***BRAF* and *NRAS* mutant subpopulation[d]**						
Selumetinib	55	42 (76.4)	275			
Temozolomide	46	27 (58.7)	383	1.621	1.18, 2.23	0.973

[a] Hazard ratio < 1 indicated a benefit for selumetinib.

[b] The 1-sided p-value indicated whether selumetinib was associated with longer time-to-death than temozolomide.

[c] Analyzed using Cox Proportional Hazards model adjusted for: lactate dehydrogenase (LDH), *BRAF* mutational status, WHO performance status and primary tumor type.

[d] Analyzed using the Cox Proportional Hazards model adjusted for: LDH and WHO performance status.

Table 3.

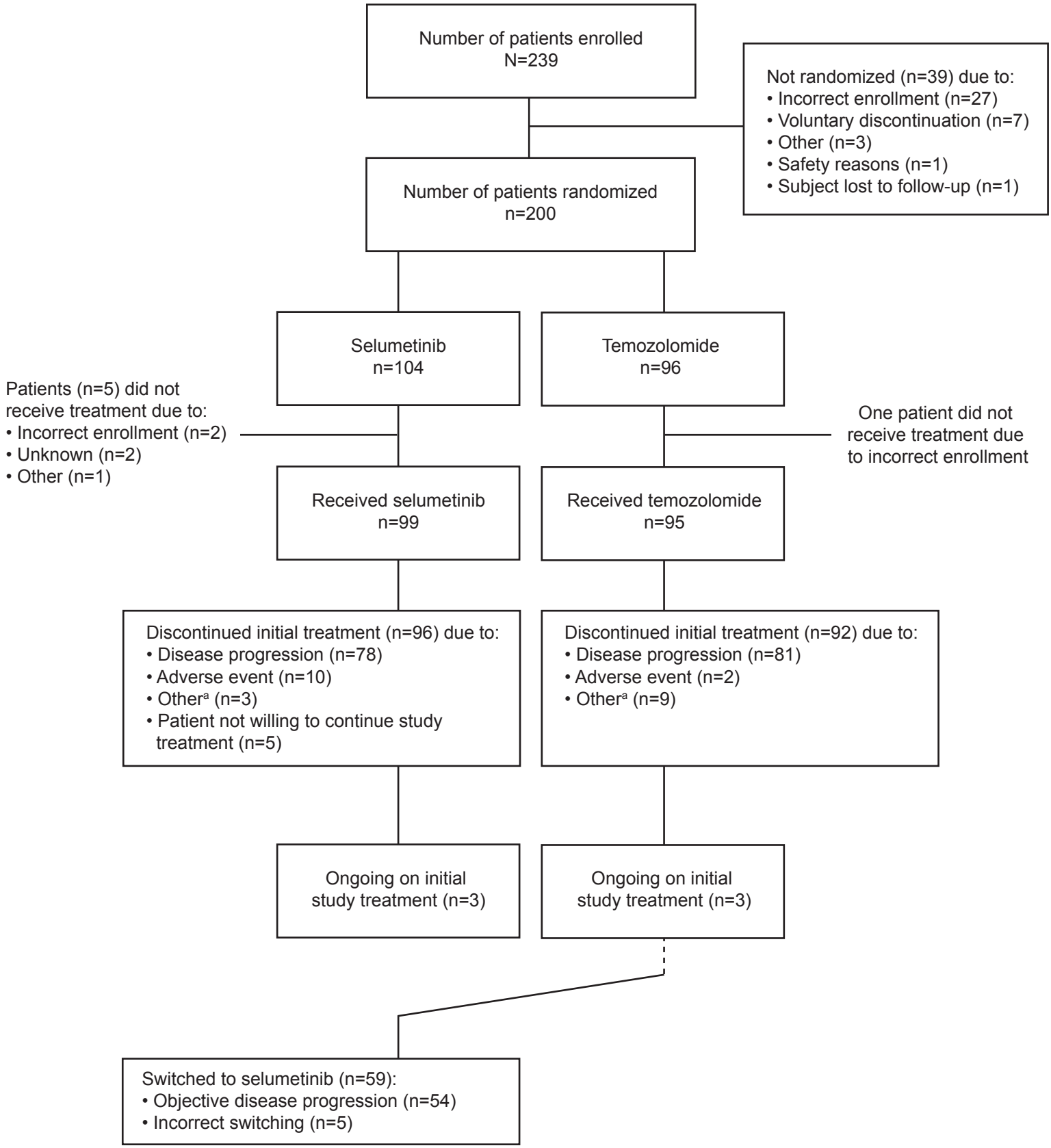
Response status	Objective tumor response	Treatment group: Selumetinib n (%)	Treatment group: Temozolomide n (%)
Overall population		**n = 104**	**n = 96**
Response[a]	Complete response	0	0
	Partial response	6 (5.8)	9 (9.4)
	Total	6 (5.8)	9 (9.4)
Non-response	Stable disease ≥ 6 weeks	48 (46.2)	36 (37.5)
	Progressive disease	40 (38.5)	43 (44.8)
	Non-evaluable	10 (9.6)	8 (8.3)
	Total	98 (94.2)	87 (90.6)
***BRAF* mutant subpopulation**		**n = 45**	**n = 28**
Response[a]	Complete response	0	0
	Partial response	5 (11.1)	3 (10.7)
	Total	5 (11.1)	3 (10.7)
Non-response	Stable disease ≥ 6 weeks	18 (40.0)	12 (42.9)
	Progressive disease	17 (37.8)	11 (39.3)
	Non-evaluable	5 (11.1)	2 (7.1)
	Total	40 (88.9)	25 (89.3)
***BRAF* and *NRAS* mutant subpopulation**		**n = 55**	**n = 46**
Response[a]	Complete response	0	0
	Partial response	5 (9.1)	4 (8.7)
	Total	5 (9.1)	4 (8.7)
Non-response	Stable disease ≥ 6 weeks	23 (41.8)	21 (45.7)
	Progressive disease	21 (38.2)	19 (41.3)
	Non-evaluable	6 (10.9)	2 (4.3)
	Total	50 (90.9)	42 (91.3)

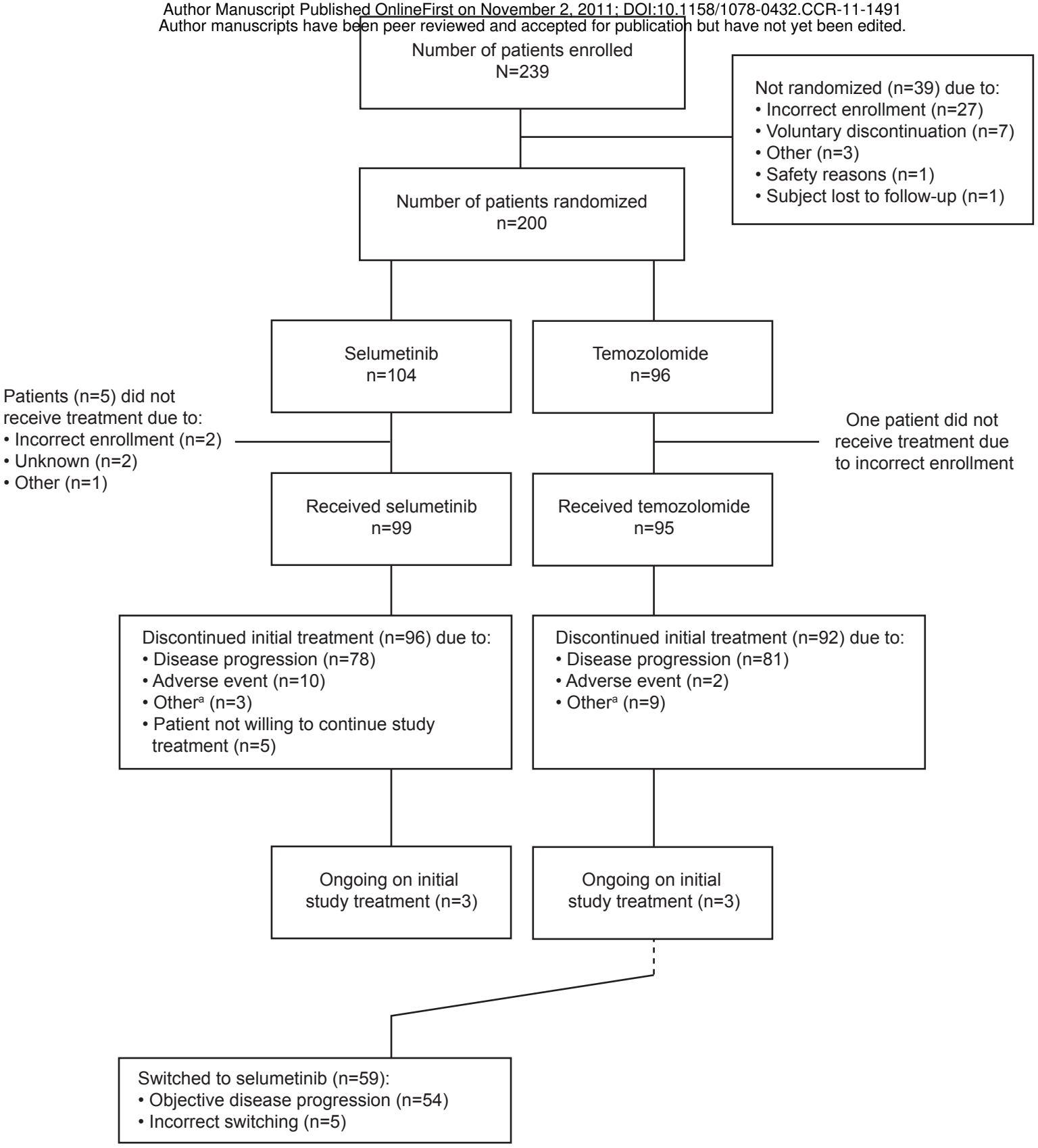
[a] An objective response included patients with either a confirmed complete response or partial response according to RECIST.

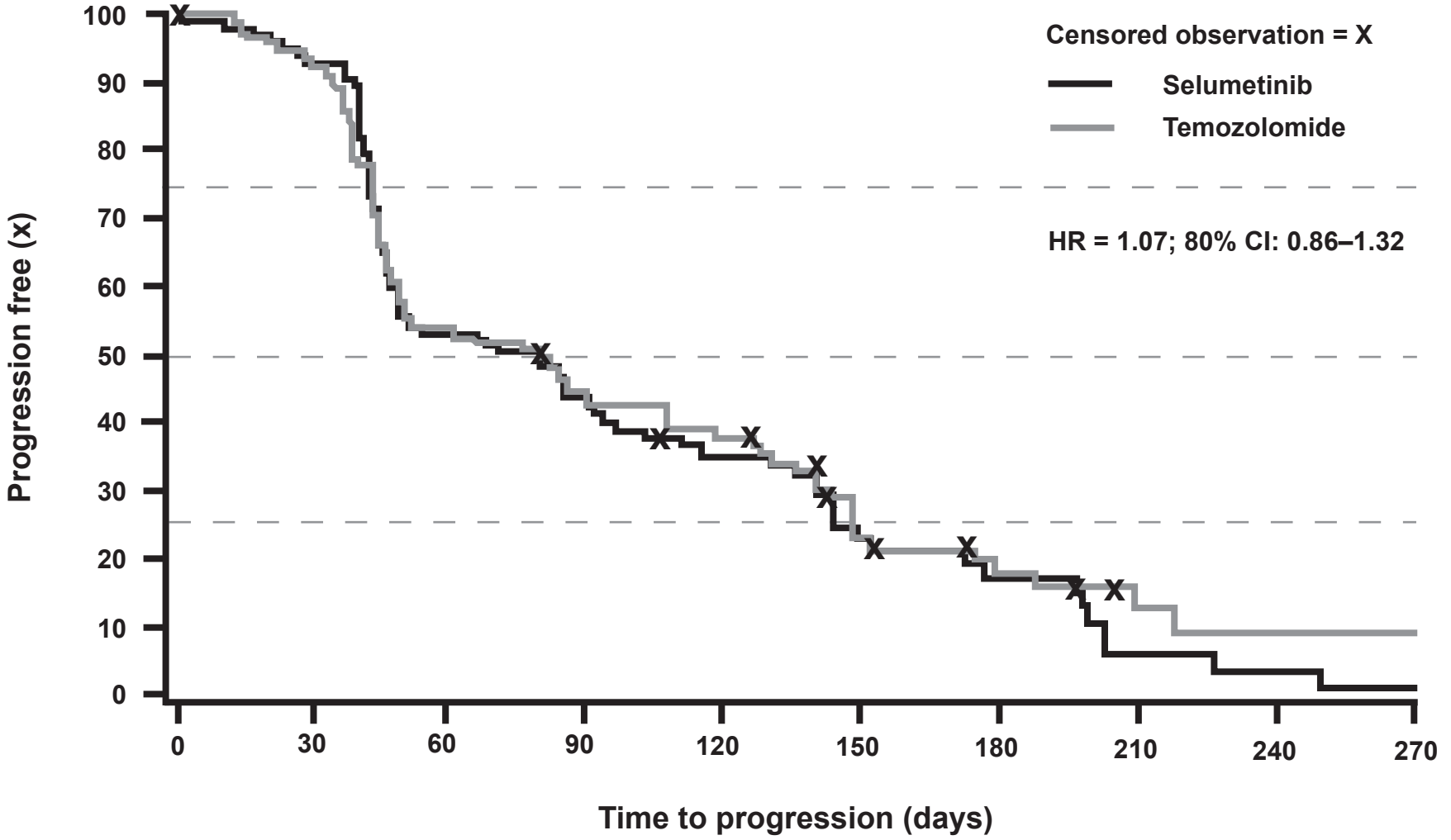
Table 4.

	Number (%) of patients			
	Selumetinib n = 99		Temozolomide n = 95	
Preferred term	**AE**	**AE ≥ Grade 3**	**AE**	**AE ≥ Grade 3**
AE	**99 (100.0)**	**57 (57.6)**	**92 (96.8)**	**36 (37.9)**
Dermatitis acneiform	59 (59.6)	12 (12.1)	3 (3.2)	0 (0.0)
Diarrhea	56 (56.6)	4 (4.0)	20 (21.1)	0 (0.0)
Nausea	50 (50.5)	3 (3.0)	61 (64.2)	3 (3.2)
Peripheral edema	40 (40.4)	1 (1.0)	6 (6.3)	3 (3.2)
Fatigue	29 (29.3)	3 (3.0)	40 (42.1)	4 (4.2)
Vomiting	28 (28.3)	1 (1.0)	42 (44.2)	6 (6.3)
Headache	21 (21.2)	3 (3.0)	23 (24.2)	2 (2.1)
Pyrexia	16 (16.2)	1 (1.0)	10 (10.5)	0 (0.0)
Constipation	12 (12.1)	0 (0.0)	45 (47.4)	1 (1.1)
Serious adverse events	**32 (32.3)**		**16 (16.8)**	
Discontinuations due to AEs	**10 (10.1)**		**2 (2.1)**	

This table includes adverse events with an onset date between the date of the first dose and 30 days following the date of the last dose of study treatment (unless the patient switched to selumetinib earlier than 30 days following discontinuation of temozolomide).

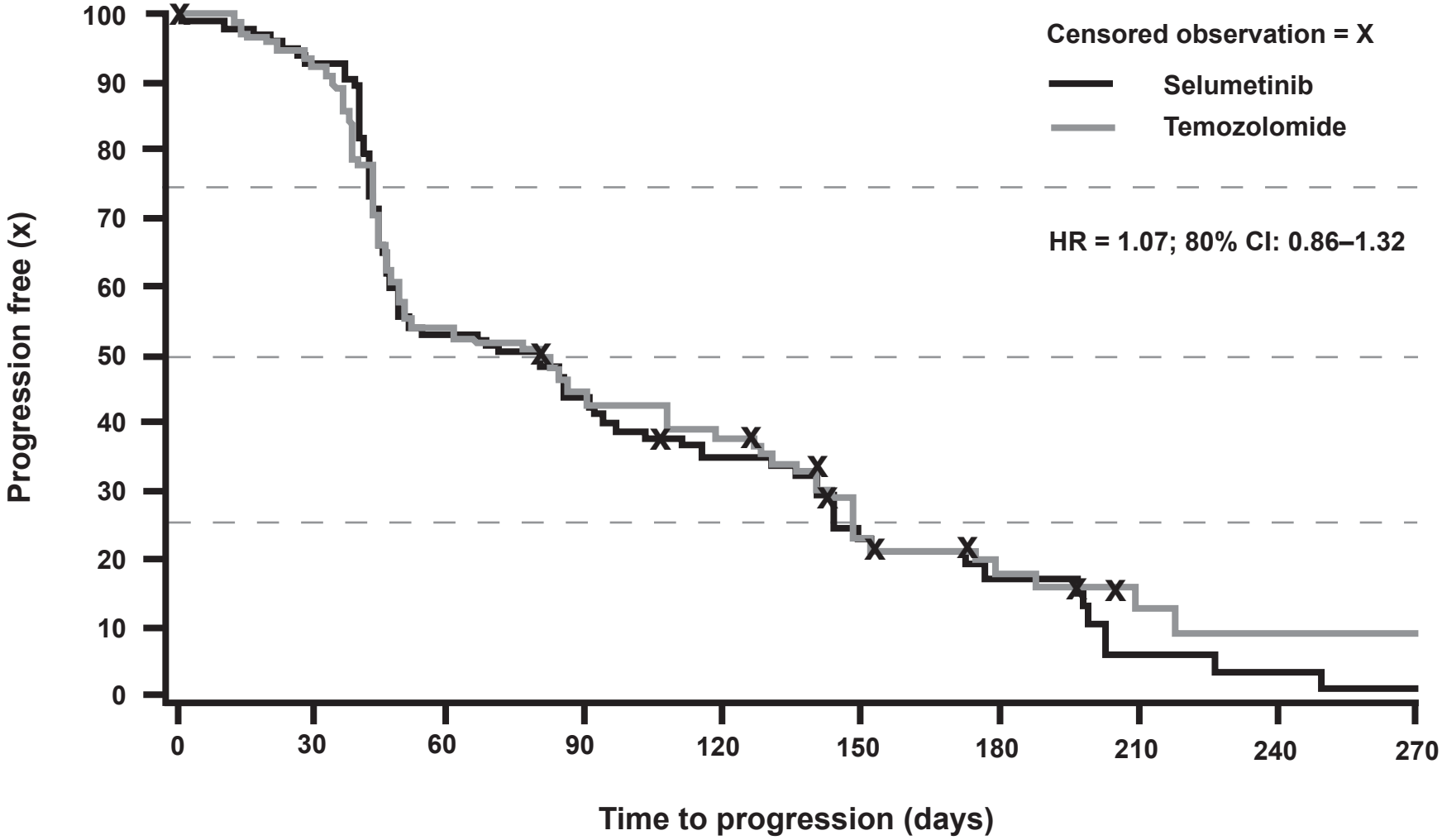






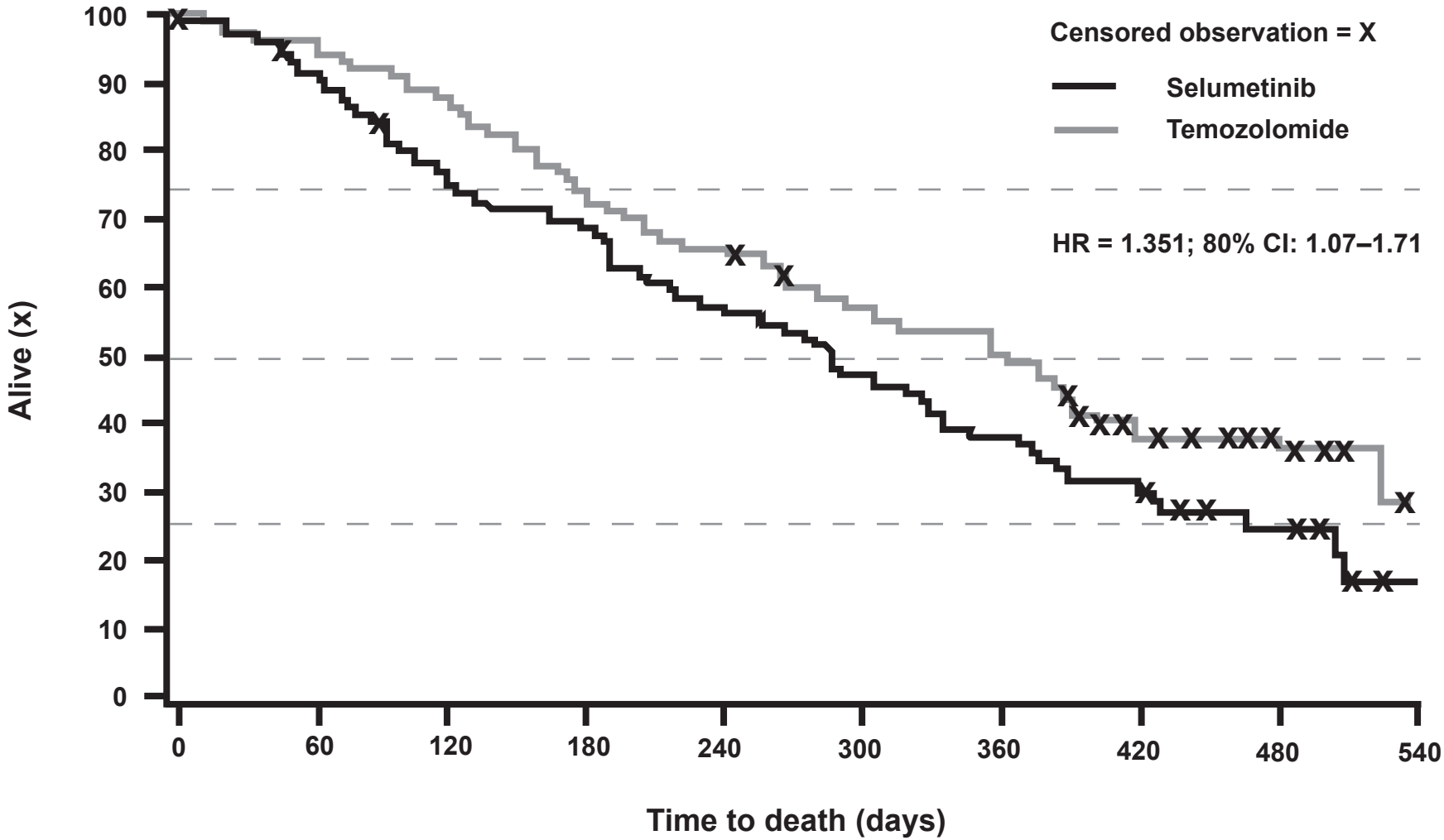
Number at risk:

Selumetinib	104	92	52	36	29	13	9	3	2	1
Temozolomide	96	86	48	32	29	12	9	4	3	3



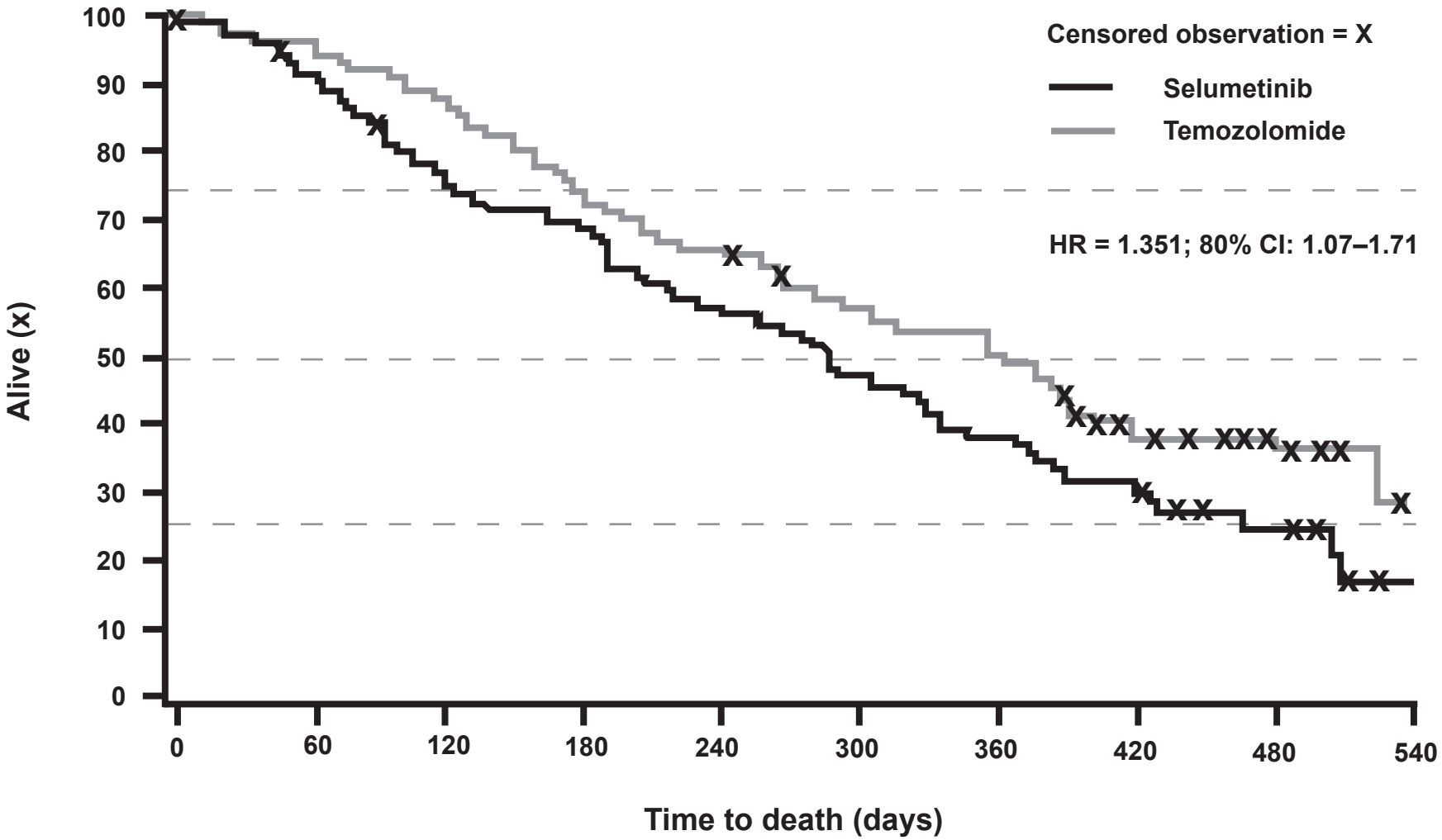
Number at risk:

Selumetinib	104	92	52	36	29	13	9	3	2	1
Temozolomide	96	86	48	32	29	12	9	4	3	3



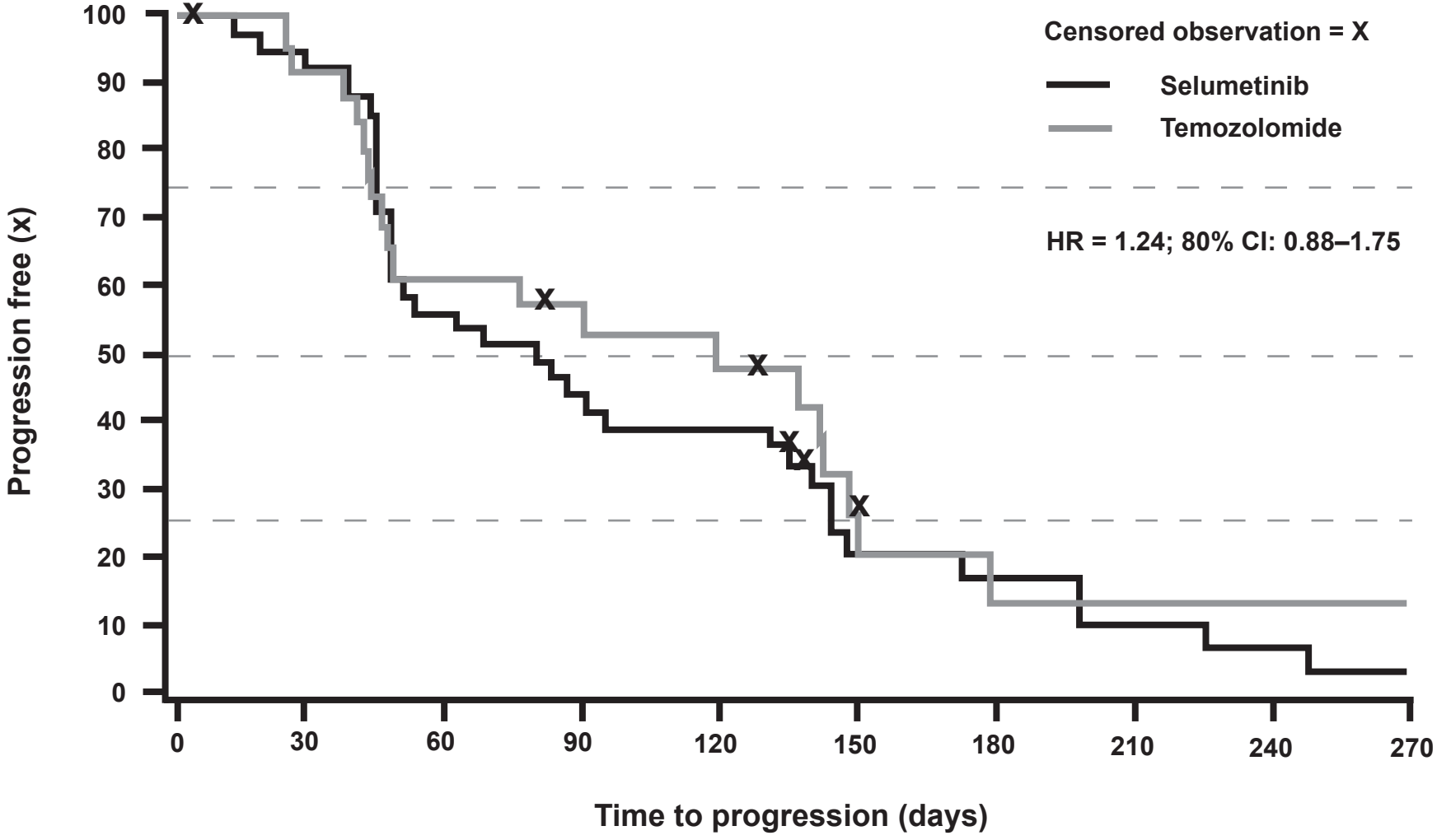
Number at risk:

Selumetinib	104	90	73	67	56	47	38	21	11	2
Temozolomide	96	90	82	68	60	52	45	24	17	3



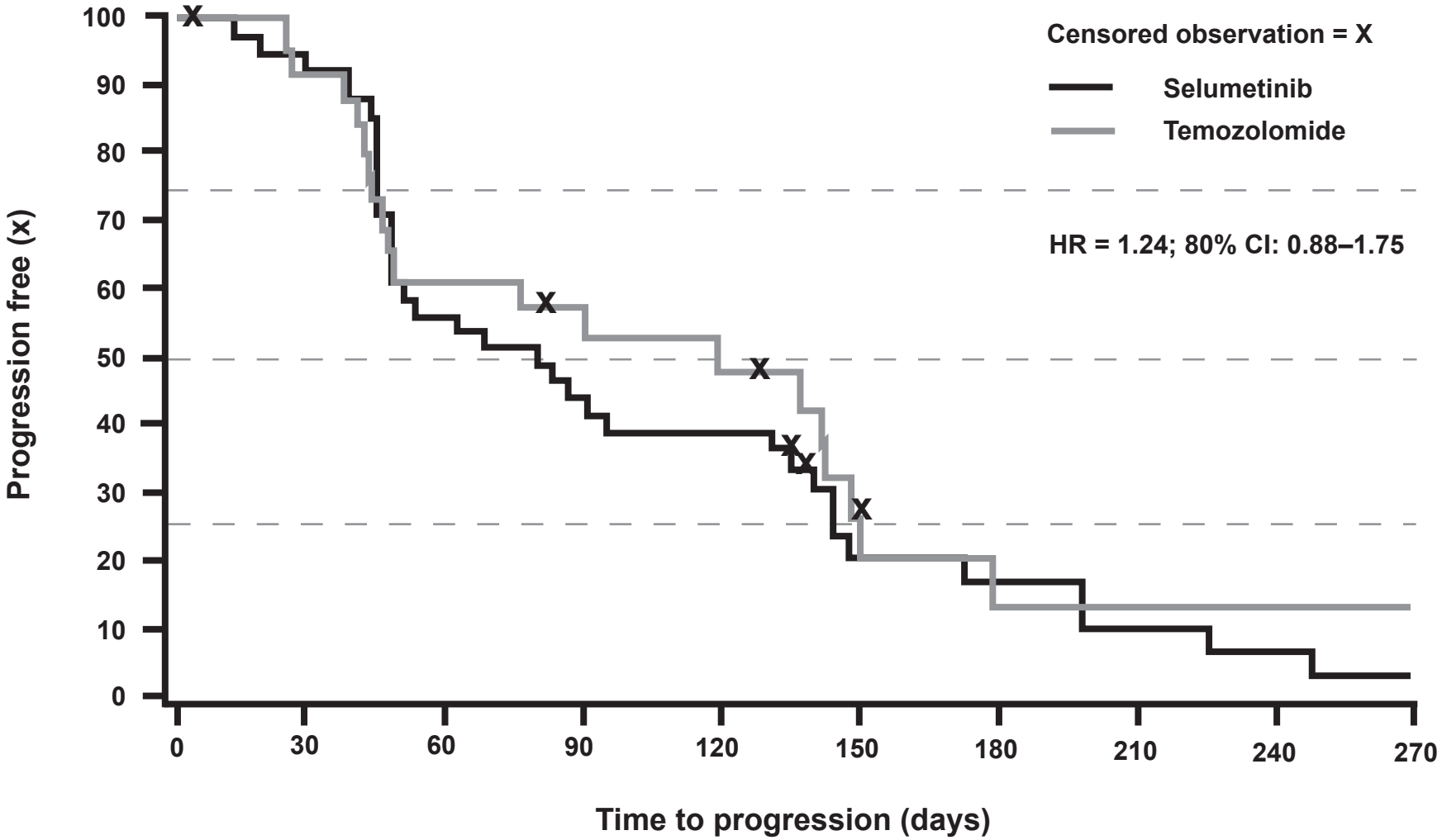
Number at risk:

Selumetinib	104	90	73	67	56	47	38	21	11	2
Temozolomide	96	90	82	68	60	52	45	24	17	3



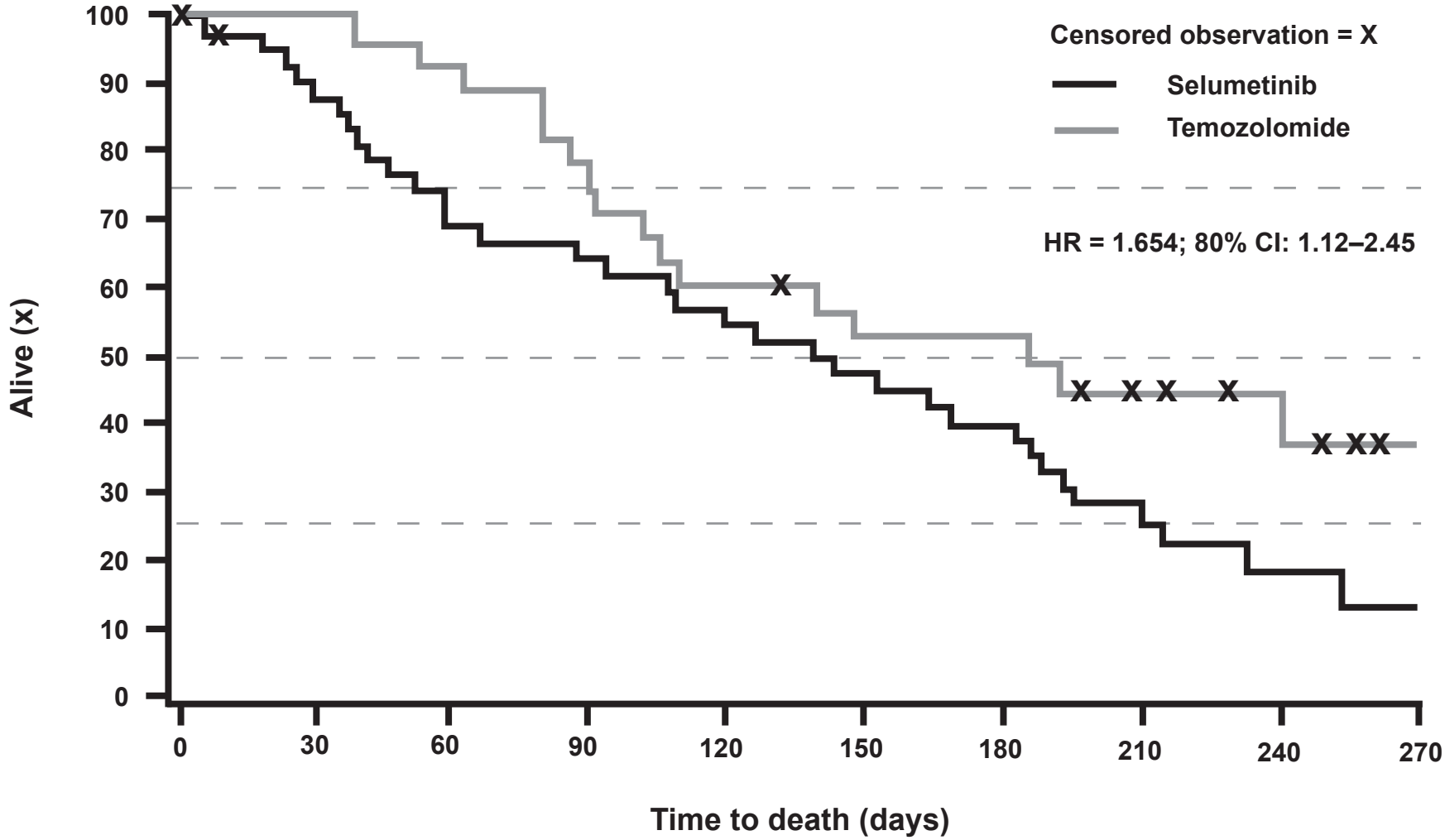
Number at risk:

Selumetinib	45	38	23	17	16	6	5	3	2	1
Temozolomide	28	24	16	11	10	3	2	2	2	2



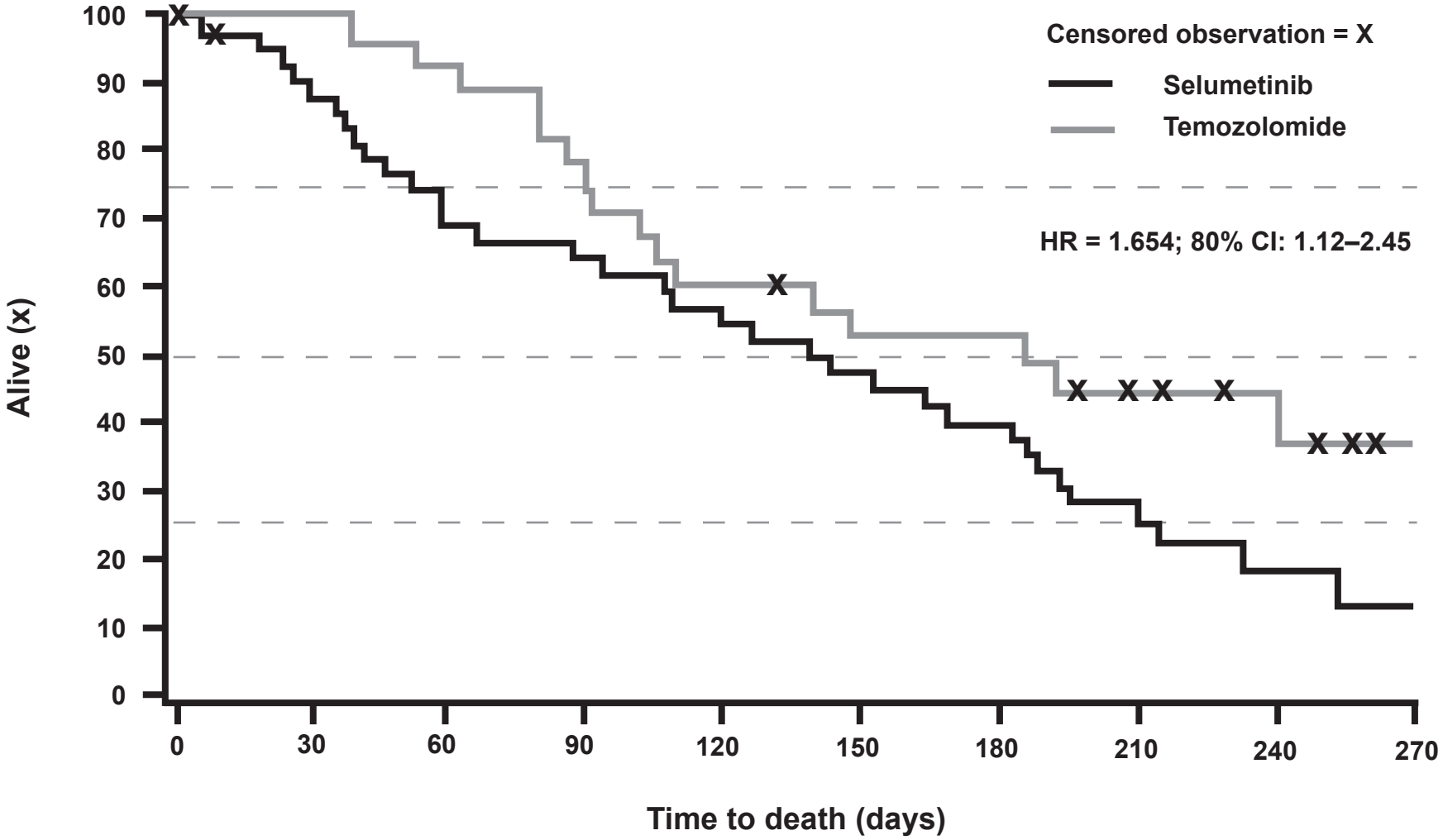
Number at risk:

Selumetinib	45	38	23	17	16	6	5	3	2	1
Temozolomide	28	24	16	11	10	3	2	2	2	2



Number at risk:

Selumetinib	45	37	29	27	23	20	17	9	5	1
Temozolomide	28	28	26	20	17	14	14	8	6	2



Number at risk:

Selumetinib	45	37	29	27	23	20	17	9	5	1
Temozolomide	28	28	26	20	17	14	14	8	6	2